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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/576,778
Filing Date: May 23, 2000
Appellant(s): SCHULEIN ET AL.

Elias J. Lambiris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 11-15-04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 62-63, 65-67, 74, 76-80.

(8) Claims Appealed

A substantially correct copy of appealed claims 62-63, 65-67, 74, 76-80 appears on page 6-8 of the Appendix to the appellant's brief. The minor errors are as follows: Claims 72-73, 75 and 81 are not part of the rejection after entry of the amendment filed on 6-22-04.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-63, 65-67, 74, 76-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme having ß 1,4-endoglucanase activity and an amino acid sequence, SEQ ID NO:2 or amino acids 1-456 or 1-617 of SEQ ID NO:2 with an optimum temperature of 65° C when measured at a pH of 7.5, active at a pH in the range of 4-11, and isolated from *B.licheniformis ATCC14580*, does not reasonably provide enablement for any such enzyme that has an amino acid sequence which is 90%, 95% or 98% identical to amino acids 1-456 or 1-617 of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 62-63, 65-67, 74, 76-80 are so broad as to encompass any ß 1,4-endoglucanase enzyme that has 90%, 95% or 98% sequence identity with amino acids 1-456 or 1-617 of SEQ ID NO:2 and has the characteristics such as an optimum temperature of 65° C when measured at a pH of 7.5, active at a pH in the range of 4-11. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of ß 1,4-endoglucanases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single ß 1,4-endoglucanase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any ß 1,4-endoglucanase having 90%, 95% or 98% amino acid

sequence identity to amino acids 1-456 or 1-617 of SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting endoglucanase activity; (B) the general tolerance of ß 1,4-endoglucanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any ß 1,4-endoglucanase amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, appellant have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including ß 1,4-endoglucanases with an enormous number of amino acid modifications of the ß 1,4-endoglucanase with amino acids 1-456 or 1-617 of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of ß 1,4-endoglucanases having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

(11) Response to Argument

In response to the above rejection, appellant has traversed and argue that the rejection under 35 U.S.C. §112, first paragraph is not proper and that claims are indeed enabled. Appellant argues that the Office has provided only arguments that the specification does not enable the claimed invention but has not provided any evidence to support its arguments. Examiner respectfully disagrees with such an argument. The Office has provided a scientific

reason to support the argument that the claims are not enabled. And that reason is that the specification has not provided specific guidance to make changes in the amino acid sequence of SEQ ID NO:2 such that the modified sequence continues to have the endoglucanase activity. It is well known in the art that making random changes in an enzyme amino acid sequence can indeed change the functional characteristic of said enzyme and may even eliminate the original activity of said enzyme. When the question of specific guidance to make the changes in the amino acid sequence is posed, all that the appellant has for support in the specification is a highly generalized guidance. Appellant points out that the techniques are routine and well known (Examiner does not question the availability of techniques to those skilled in the art), such as methods to prepare cDNA libraries, PCR, site directed mutagenesis, shuffling etc. Next, appellant indicates that a table defining conservative amino acid substitutions is provided at page 12 and reference to a number of patents on page 14 describing the shuffling methods. Appellant argues that using such methods one of ordinary skill in the art will be able to routinely produce thousands of mutants in a short period of time and further would be able to identify the claimed enzyme. Examiner respectfully disagrees with above arguments. Regarding the availability of techniques to make changes in an amino acid sequence, Examiner indeed has indicated that methods to make changes in an amino acid sequence are well known. However, specific guidance is required to pick and choose only those amino acids in the enzyme sequence that can be modified, as well as guidance regarding the amino acid/s (from among the twenty naturally occurring) that can be used for replacement or substitution. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities (i.e., replacing every one of the 617 amino acids with any one of the twenty

other amino acids followed by testing each and every sequence for the activity). Contrary to the appellant's argument that this would be routine, it would clearly constitute undue experimentation. Appellant argues that some experimentation like carrying out a simple process without special equipment and reaction conditions would be necessary and that such experimentation would not be undue. Examiner respectfully disagrees with such an argument. This is because the protein in question is a fairly large protein comprising at least 456 amino acids and up to 617 amino acids. Appellant's argument that for a protein of such size, the experimentation would not be undue is a highly misplaced argument.

Next, appellant refers to Appendix 2 which is nothing but a compilation of BLAST search. Appellant has searched different enzymes and argues that the results show clearly and convincingly that one of ordinary skill in the art would expect that proteins having 90% sequence identity would have the desired function/utility. It is not clear to the Examiner as to what is the point of the Appendix 2 which comprises the sequence comparisons of proteins isolated from their natural sources. All that the Table in Appendix 2 does is indicate the existence of enzymes with similar function from different sources. It does not provide any guidance to those skilled in the art to make any type of amino acid changes in SEQ ID NO:2. It is not at all clear to the Examiner as to how the information in Appendix 2 points to any type of guidance that can be used to make changes in the instantly claimed SEQ ID NO:2.

Next, appellant brings in the reference of Wilson et al. and argues that said reference establishes a clear relationship between sequence similarity and functional similarity. Appellant argues that Wilson et al. found that functional identity is conserved down to approximately 40% amino acid sequence identity and that among proteins that share 50-100% sequence identity,

function is conserved in almost all, and therefore, it is not "unpredictable" to make base changes and maintain desired activity/utility as suggested by the Examiner. Appellant further goes on and argues that the Office's arguments are misplaced because the specification on pages 13-14 discloses that one of ordinary skill in the art can readily identify essential amino acids and the active site in SEQ ID NO:2 by methods well known in the art and that while some experimentation may be necessary such experimentation would not be undue. Examiner respectfully disagrees with such arguments as being persuasive to overcome the above rejection. The teachings of Wilson et al. reference does little or nothing at all in answering the Examiner's question of specific guidance to make amino acid changes in SEQ ID NO:2. First of all the Wilson et al. reference is a highly generalized reference and is not devoted specifically to endoglucanases. Furthermore, the reference has laid down conditions for the proteins to be similar which the appellant has conveniently ignored. For example, the reference clearly teaches that for pairs of domains that share the same fold, precise function appears to be conserved to ~40% sequence identity, whereas broad functional class is conserved to ~25%. Thus, it is clear to those skilled in the art that information on how the protein folds is required in order to accept Wilson et al.'s conclusion. Without the three dimensional information on protein folding, the teachings of Wilson et al. cannot be applied to any protein. In the instant case, appellant has not provided any information regarding the sequences in SEQ ID NO:2 that are involved in folding and their resistance to change.

In conclusion, Examiner reiterates that the specification fails to provide specific guidance to make amino acid changes in SEQ ID NO:2 and without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite

possibilities (i.e., replacing every one of the 617 amino acids with any one of the twenty other amino acids followed by testing each and every sequence for the activity). Furthermore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting endoglucanase activity; (B) the general tolerance of ß 1,4-endoglucanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any ß 1,4-endoglucanase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Art Unit 1652

February 2, 2005

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